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EXAMINER	
SHUKLA, RAM R	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/002,244	GILMAN ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *1-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of the invention of group II, claims 18-37, in Paper filed 9-22-2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-17 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper filed 9-22-2003.

3. This application is a continuation application of USSN 08/672,21 3 filed June 27, 1996 and is a continuation in part of USSN 09/407,402 filed September 28, 1999, which was a continuation in part of USSN 09/262,721 filed March 4, 1999, which was a continuation in part of USSN 09/096,732 filed June 11, 1998, which was a continuation of USSN 60/000,553, filed June 27, 1995 and USSN 60/019,614, filed December 29, 1995, the full contents of which are incorporated herein by reference.

Claim Objections

4. Claims 1, 25, and 27 are objected to because of the following informalities: The claims contain the following typographical errors: in claim 18, on line 6, the term "trancription". Appropriate correction is required.

Claim 25 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim (claim 24). Claim 24 limits the invention of claim 24 by reciting what is comprised in the transcription factor. Claim 25 dependent on claim 24 does not limit the invention of claim 24.

Claim 27 is objected to under 37 CFR 1.75(c), as being improper dependent form for failing to further limit the subject matter of a previous claim (claim 26).

Claim 26 is directed to the p65 peptide region 361-450 and claim 27 is directed to the p65 peptide region 361-550.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Double Patenting

5. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

6. Claims 33, 36 and 37 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 and 2 of prior U.S. Patent No. 6,306,649 B1. This is a double patenting rejection.

Claims 1 and 2 of the cited patent are drawn to the same invention as the invention of claims 36 and 37. It is noted that while claim 33 of the instant application is broad, it is included in the rejection because it will be encompassed by the invention of claim 36.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claim 37 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claim is directed to non-statutory subject matter because the claim reads on a cell occurring in a human host *in vivo*. Claiming a cell within a human gives exclusion rights to that human, and any claims to humans is non-statutory by PTO policy. (See 1077 OG 24, April 21, 1998). Recitation of the term "isolated" in the claim would overcome this rejection.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 18-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention encompasses (i) a method for expressing a target gene in a cell within a host organism which comprises introducing into the cells of the organism cells: (a) any transcription factor construct containing a first heterologous DNA sequence encoding and capable of expressing any transcription factor capable of activating transcription of a gene linked to a transcription control sequence responsive to the transcription factor, and (b) a target gene construct containing a second heterologous DNA sequence comprising a target gene operably linked to a transcription control sequence comprising any DNA promoter sequence and one or more copies of any DNA recognition sequence permitting gene transcription responsive to the presence of the transcription factor; wherein the organism may be a mammalian or human. The transcription factor may be any transcription factor, any transcription control sequence, any DNA recognition sequence, any naturally occurring human peptide sequence, any composite DNA-

binding domain, any transcription activating protein of human origin. These compositions encompass a broad genus of compositions. However, the specification as filed only teaches NF-Kb p65 sequence structure for a transcription factor and VP16 V8, VP16 C, HSF and CTF as the transcription activation peptide sequence.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the complete structure of NF-KB (transcription factor) and VP16 V8, VP16 C, HSF and CTF (transcription activation peptide) only has been disclosed. The specification does not provide any disclosure as to what would have been structure of representative number of transcription factors and of transcription activation proteins. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification does not describe any relevant identifying features of the representative number of species of the claimed genus.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of the sequence of NF-KB transcription factor and transcription activation peptides VP16 V8, VP16 C, HSF and CTF, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

11. Claims 18-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Instantly claimed invention encompasses (i) a method for expressing a target gene in a cell within a host organism which comprises introducing into the cells of the organism cells: (a) any transcription factor construct containing a first heterologous DNA sequence encoding and capable of expressing any transcription factor capable of activating transcription of a gene linked to a transcription control sequence responsive to the transcription factor, and (b) a target gene construct containing a second heterologous DNA sequence comprising a target gene operably linked to a transcription control sequence comprising any DNA promoter sequence and one or more copies of any DNA recognition sequence permitting gene transcription responsive to the presence of the transcription factor; wherein the organism may be a mammalian or human and composition of DNA sequence encoding a chimeric transcription factor that comprises all or part of the peptide sequence spanning aa 361-550 construct and a peptide sequence heterologous thereto. The transcription factor may be any transcription factor, any transcription control sequence, any DNA recognition sequence, any naturally occurring human peptide sequence, any composite DNA-binding domain, any transcription activating protein of human origin. The methods are for practicing in any organisms, any mammals or human. Dependent claims limit different parameters. Since the method is for expressing a protein in an organism it is interpreted as an in vivo method. Since the only utility disclosed in the specification is for gene therapy, the claims have been interpreted for gene therapy.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been

provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification discusses that the claimed methods are useful for applications ranging from gene therapy to the production of biological materials and biological research. In particular, the specification discusses the applicability of the claimed methods for gene therapy. See pages 1, 4 and 28-29 of the specification. See the Title of the invention, Use of Heterologous Transcription Factors in Gene Therapy. See also claims 3 and 20 which are specifically limited to employing the claimed methodology in humans. Although the claimed methods are not limited to any particular application requiring any particular effect (therapeutic or not), with regard to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest reasonable interpretation of the claimed invention encompasses a method for expressing a target gene in a cell within a host organism (a human host) to achieve expression of the target gene at a level resulting in a therapeutic effect. For this embodiment the claimed invention is not enabled by the specification.

The specification specifically teaches the construction of DNA plasmids encoding DNA-binding and transcription activating fusion proteins, *e.g.*, GAL4-FRAP, FRAP-VP16, ZFHD1-FRAP, FRAP-p65, to create a representative final construct, pCGNN-ZFHD1-1FRB. The specification teaches the construction of a retroviral vector, SMTN-ZFHD1-3FKBP. The specification teaches cell culture experiments demonstrating rapamycin-dependent transcriptional activation of reporter gene constructs using transient or stable cell transfection assays employing the DNA plasmids encoding the fusion proteins and the DNA plasmids encoding the reporter genes. The specification further demonstrates rapamycin-dependent production of hGH in nude mice by i.m. transplantation of the cells transfected with the above constructs. The specification additionally teaches cell culture assays using DNA constructs encoding hybrid transcription factors for constitutive expression of the reporter gene construct. See representative results of chimeric transcription factors on page 57 of the specification.

Such cell culture and nude mouse assays for regulated or constitutive levels of reporter gene expression do not provide a prediction of therapy for any disease. Applicants fail to provide a correlation to levels of expression of any particular therapeutic target gene of interest in the transfection assays of the instant application, in particular in methods of *ex vivo* gene transfer. The status of the gene therapy art, in particular, at the time of the effective filing date of the claimed invention, was undeveloped and unpredictable in terms of achieving *in vivo* expression levels of a gene of interest. Orkin et al. (1995) support such an observation, who state:

2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

3. Significant problems remain in all basic aspects of gene therapy.

Orkin et al. further report the difficulty of extrapolating from experiments in animal models to human studies, in particular with respect to the efficiency of gene delivery and the host response to viral vectors. See page 14, 4th paragraph. To this regard, MPEP section 2164 sets forth that the issue of "correlation" is also dependent on the state of the art at the time of the invention. MPEP, section 2164 goes on to discuss that if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention broadly pertains, then there is lack of predictability in the art. Thus, what is known in the art provides evidence as to the question of predictability.
Additionally, Crystal (Crystal RG. Science 270:404-410.1995) assessed the state of the art of the gene therapy at the time the claimed invention was made. In the abstract, Crystal states, "human gene therapy still faces significant hurdles before it becomes an established therapeutic strategy". Later on page 409, he summarizes the problems faced in the art of gene therapy, such as inconsistent results, extrapolation of studies in mice to humans, production, and vector. He states, " all of the human gene transfer studies have been plagues by inconsistent results, the bases of which are unclear" (see para 3 in col 1 on page 409). He also adds that there are several examples wherein prediction of gene transfer studies in experimental animals have not be borne out in human trials (see para 4 in col 1 on page 409). He also raises the issue of production of vectors, free of aggregation, contamination and variability from preparation to preparation, some of the problems that must be overcome before large clinical trials can be initiated. Additionally, there is the issue of an ideal vector? Crystal argues that an ideal vector for gene therapy is conceptually impractical because the human applications of gene transfer are broad and the ideal vector will likely be different for each application (see col 2 on page 409).

Even in 2000, the state of the art of gene therapy was unpredictable as discussed by Romano et al, Romano et al (Romano et al. Stem Cells 2000; 18:19-39) reporting on the recent developments of gene therapy, noted, "However, the real effectiveness of gene therapy programs is still in question. After a decade of

clinical trials, the therapeutic applications of gene transfer technology are still at a rather preliminary stage."

It is noted that these reviews by the leaders in the field of gene therapy are about those gene therapy protocols and applications where the mechanism of action and some efficacy has been determined in animal models and there may be some extrapolatable correlations indicating the therapeutic effects of a particular gene's encoded protein. Even with such results, it is uncertain whether there would be a therapeutic effect when the studies obtained in a mouse model or another animals model is extended to a human subject.

Accordingly, it is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Furthermore, case law has established that in terms of predictability, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof, In re Marzocchi , 439 F.2d 220, 223 - 24, 169 USPQ 367, 368 - 70 (CCPA 1971). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). In the instant case, there is no evidence or reasonable correlation thereto in the specification which supports the production of levels and duration of expression of any therapeutic target gene of interest sufficient to provide treatment by means of the claimed methodology. Applicants merely demonstrate rapamycin-dependent hGH gene transfer in nude mice which can be assayed for to detect minimal levels of expression. Accordingly, such a demonstration fails to provide correlative evidence of sufficient levels of expression of a target gene of interest .

With regard to *in vivo* gene expression, numerous factors complicate gene therapy with respect to predictably achieving levels and duration of expression

which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. See Eck and Wilson, 1995, page 82, column 1, first paragraph. These factors differ dramatically based on the vector used, the route of administration of the vector, the protein being produced, and the disease and/or host being treated. The specification fails to provide guidance for any of the above parameters for *in vivo* or *ex vivo* gene therapy and only teaches regulated expression of a hGH target gene in nude mice by intramuscular transplantation of cells transfected with the constructs encoding the fusion transcription factors (ZFHD-FKBP or FRB-p65) of the invention. The claims encompass any route of administration, however, the specification specifically teaches intramuscular transplantation and fails to teach how cell-targeting may be accomplished to specific tissue or cell types using other routes of administration. For the treatment of a wide range of diseases, cell targeting and other routes of administration of the fusion constructs of the invention would be necessary, however, Applicants fail to teach or provide a reasonable correlation thereto any route of administration or any cell-targeting techniques which effectively target expression of a gene of interest to any particular cell type at levels sufficient to cause a therapeutic effect. Orkin et al. clearly support that cell-targeting methodology is undeveloped at the time of the invention. Specifically, Orkin et al. discuss that cell targeting methodologies have not yet reached clinical application and that research in these areas within the context of gene therapy strategies is in its infancy. See page 8, last paragraph and paragraph bridging pages 9-10.

Even if Applicants wish to limit the claimed invention to cell culture methods, the scope of the DNA constructs of the claimed methods is not commensurate with the teachings of the instant specification. The claimed invention encompasses an

enormous number of possible combinations and arrangements of DNA sequences encoding transcription factors or composite transcription activation domains, and target gene sequences in operable linkage with promoter sequences and DNA recognitions sequences. The prior art indicates that the creation of functional chimeric proteins containing DNA-binding domains or transcriptional activation domains is unpredictable. See, e.g., Orloff et al. (Nature, 1990), Lui et al. (Immunology Today, 1993), Weintraub et al. (Science, 1991), Bergmann et al. (J. Steroid Biochem. Molec. Biol., 1994), Qi et al. (Molecular and Cellular Biology, 1995) and Sadowski et al. (Nature, 1993). Collectively, the prior art supports that transcriptional activator domains and DNA binding domains are not freely interchangeable to produce chimeric proteins that are capable of transactivation (which is required for promoting target gene expression). Furthermore, on page 57 of the specification, Applicants list chimeric transcription factors which fail to activate transcription and constitutive expression of the target marker gene in cell culture methods of the invention, *e.g.*, GAL4-p65 (361-450), GAL4Oct2 Q domain (aa95-160), GAL4-Oct2 P domain (aa438-479), and GAL4-EWS11 (SRSYGQQGSGS). The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. *Ex parte Maizel,* 27 USPQ2d 1662 (BPAI 1992). As such, Applicants provide no nexus between the DNA constructs employed in the examples and DNA constructs encoding transcriptional activation domains known in the prior art and demonstrated to be unpredictable in terms of activating transcription, or DNA constructs that have yet to be developed by trial and error experimentation by identifying and isolating cellular transcriptional activation components for the construction of recombinant DNA constructs which encode the components which may activate transcription of a target gene of interest. As such, the skilled artisan would have to partake in undue experimentation without a reasonable expectation of identifying, isolating, combining and arranging DNA constructs which encode the components essential for the activation of transcription of a target gene of interest.

Accordingly, claims 1-32 are rejected under 35 U.S.C. §112, first paragraph, as being non-enabled by the specification.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 is incomplete because they do not recite that the target gene is expressed in a cell within the host organism.

In claims 18 and 31, the recitation of "permitting gene transcription", "permitting DNA uptake", and "permitting gene expression" is vague and indefinite because the claim does not indicate which gene, genes, or DNAs are permitted to be transcribed or expressed, etc.

In claims 1 and 18, the recitation of "capable of" renders the claims indefinite because the capacity of a compound to perform some function is merely a latent characteristic of said compound and said language carries no patentable weight. See MPEP §2173.05(b), (d) and (g). Deletion of the recitation of "capable of" would overcome this rejection.

In claims 18, 29, 30, 33, 35, and 36, the recitation of the term "heterologous" is vague and indefinite with respect to DNA and peptide sequences as the meaning of the term is not clear in the context of the claims. In particular, it is noted that dependent claims further limit the host and peptide sequences to human. However, in this context, how would the DNA and peptides encoded by the DNA derived from human origin, be heterologous to a human host?

In claims 25, 26, 29 and 33, the recitation of the limitation "all or part of the peptide sequence spanning positions 361 through 550 of the human NF-kB p65, or a peptide sequence derived therefrom" is vague and indefinite because it is unclear

what metes and bounds of the phrase "a peptide sequence derived therefrom" pertains to as the claim already recites "all or part of the peptide sequence spanning positions 361 through 550 of the human NF-kB p65".

In claims 25, 26, 29, 30, 33, and 36, the terms "NF-kB", "VP16 V8", "VP16 C", "HSF", "CTF", are vague and indefinite because the ordinary artisan would not know the technical designation of these abbreviated terms unless recited in the claims.

In claims 29 and 35, the recitation of "potentiates" and "potentcy" is vague and indefinite because neither the claims nor the specification define what criteria constitutes what is encompassed within the metes and bounds of the terms.

In claim 19, the recitation of "under conditions permitting DNA uptake by one or more cells" is vague and indefinite because neither the claim nor the specification define conditions for the DNA uptake by one or more cells.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Fishman et al (Journal of Clinical Investigation 93:1864-1868, 1994).

Fishman et al. teaches a regulatable gene expression system comprising (1) a tet repressor-VP16 transactivator expression plasmid and (2) a luciferase expression plasmid comprising a tet operator in its promoter region. Fishman et al. teach injection of said plasmids into cardiac muscle of a rat and show that oral tetracycline efficiently induces expression of the luciferase gene in the treated rat's cardiac cells (pp. 1864-6).

16. Claims 33, 34 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmitz et al (The EMBO Journal 10:3805-3817, 1991).

Schmitz et al. teach recombinant DNA molecules encoding polypeptides comprising a DNA-binding domain of GAL4 protein and portions of human NF-κB p65 comprising residues from the regions 361-450 and 361-550 (pp. 3808-11). Schmitz et al. also teach co-transfection of cells with said DNA molecules and a CAT reporter construct with GAL4-binding sites in the promoter region. Schmitz et al. further teach that residues 521-550 of NF-κB comprise a strong transactivating domain, TA_1, and that a second transactivating domain, TA_2, is present in residues 441-518 (p. 3809).

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 18-19 and 33-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al and Schmitz et al in view of Evans et al (US 5,597,693; US 5,262,300 and US 5534,418).

Fishman et al. teaches a regulatable gene expression system comprising (1) a tet repressor-VP16 transactivator expression plasmid and (2) an expression plasmid comprising in its promoter a response element bound by said DNA-binding

domain, for regulated expression of the gene encoded by said expression plasmid (b) in cells of an animal, as discussed above(pp. 1864-6).

Schmitz et al. teach making recombinant DNA molecules encoding fusion transcription factors comprising a DNA-binding domain of GAL4 protein and a portion of NF-κB p65 comprising transactivating domain TA_1, located in residues 521-550, or TA_2 located in residues 441-518, and a method wherein cells are co-transfected with one of said DNA molecules and with a CAT reporter construct having GAL4-binding sites in the promoter region to effect expression of the reporter gene in said cells, as discussed above. Schmitz et al. also teach that a chimeric transcription factor consisting of the DNA-binding domain of GAL4 protein and the transactivating domain of VP16 is a stronger inducer of transcription than any of the GAL4-p65 constructs which they tested (p. 3810).

Fishman et al. and Schmitz et al. do not teach constructs wherein the DNA-binding domain is a domain of a human protein or is a composite DNA-binding domain, or wherein the transcription factor comprises a composite transactivation domain such as a fusion comprising transactivation domains from both human NF-κB p65 and VP-16.

Evans et al. (US Pat. 5,597,693) teach that domains of steroid receptors are interchangeable, and that the DNA-binding domain of the human glucocorticoid receptor can be replaced by that of the thyroid hormone receptor to produce a hybrid protein which binds and activates promoters comprising a thyroid hormone receptor response element (col. 9, lines 40-43). They also demonstrate that a transcription factor comprising a composite DNA-binding domain made up of portions of two different human steroid receptors functions effectively in cells to activate a gene promoter comprising a response element which is recognized by said composite DNA-binding domain (Example 2, columns 9-10).

Evans et al. (US Pat. 5,262,300) disclose transcription factors having a composite transactivating domain comprising (a) multiple copies of one or more transactivating regions of a given human steroid receptor, or (b) a transactivating region of a human steroid receptor and also comprising a synthetic acidic peptide which has transactivating activity, and they show that both types of transcription

factors function effectively in cells to activate a gene promoter comprising a response element which is recognized by said transcription factors (column 12, line 46, to col. 13, line 9).

Evans et al. (US Pat. 5,534,418) teach using a gene expression system comprising (a) a vector encoding a steroid receptor-type transcription factor, and (b) an expression plasmid comprising in its promoter a response element which is bound by the DNA-binding domain of said steroid receptor-type transcription factor, to obtain regulated expression of the gene encoded by said expression plasmid (b) in cells of an animal (col.s 19-20).

At the time the application was filed, it would have been obvious to one of ordinary skill in the art to modify the vector of Fishman et al and Schmitz et al to make a vector that comprises a nucleic acid encoding a transcription factor comprising a DNA-binding domain of a human transcription factor or a vector encoding a transcription factor comprising a composite DNA-binding domain or a composite transactivating domain,, for example, of one of the numerous transcription factors of the steroid receptor family disclosed by Evans et al., given the teaching by Evans et al. that such sequence-specific DNA-binding domains can be interchanged between proteins with retention of function and that a transcription factor comprising a composite DNA-binding domain or a composite transactivating domain functions more effectively to activate transcription in a cell.

It would have been obvious to one of ordinary skill in the art to make a vector wherein the transcription factor comprises a portion of the region 361-450 of human NF-κB p65, and further comprises a transactivating domain of VP-16, given the teaching by Schmitz et al. that both of said polypeptide domains have transactivating activity, and the teaching by Evans et al. that a transcription factor comprising a composite transactivating domain functions effectively to activate transcription in a cell, so that one of ordinary skill in the art would reasonably have expected the method using said human NF-κB p65-VP16 composite transcription factor to function successfully to activate gene transcription in a cell in the same effective manner shown for other chimeric transcription factors as taught by Fishman et al., Schmitz et al., and Evans et al. as discussed above. Thus, the

invention as a whole stands as being clearly prima facie obvious in the absence of evidence to the contrary.

20. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for TC 1600 is (703) 703-872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

Please note that effective January 13, the offices for Examiner Shukla, SPE Reynolds and LIE William Phillips will move to the new USPTO location in Alexandria, VA and their phone numbers will change. The new phone numbers will be as follows:

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